

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: RITA MITRA Examiner #: 77995 Date: 9/3/02
 Art Unit: 1653 Phone Number 301 605-1211 Serial Number: 09/599463
 Mail Box and Bldg/Room Location: 9B01 CMI/ 9B03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

 Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: "Recombinant Protein Production in Human cell"

Inventors (please provide full names): Guus Hatteboer, Karina Cornelia Verhaulst, Govert Johan Schouten, Alphonsus Gerardus Dytelchak, Abraham Bont Moerkapelle

Earliest Priority Filing Date: 4/15/1999

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

I request a search (Patent and Nonpatent literature) on this case.

The search should encompass a method of producing proteinaceous substance in a eukaryotic cell wherein said proteinaceous substance comprises a viral protein (cl 77), wherein the viral protein is from Influenza Virus (selected in cl 82)

Keywords:

- A denoviral E1 protein and E1A protein
- post translation and pre-translation modification
- erythropoietin

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	Type of Search	Vendors and cost where applicable
Searcher: <u>9-11-02</u>	NA Sequence (#) _____	STN <u>328</u>
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Date Completed: <u>9-11-02</u>	Litigation _____	Lexis/Nexis _____
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Bib Data Sheet

SERIAL NUMBER 09/549,463	FILING DATE 04/14/2000 RULE -	CLASS 514	GROUP ART UNIT 1614	ATTORNEY DOCKET NO. 4038.1US
APPLICANTS Guus Hatteboer, Heemstede, NETHERLANDS; Karina Cornelia Verhulst, Leiden, NETHERLANDS; Govert Johan Schouten, Leiderdorp, NETHERLANDS; Alphonsus Gerardus Uytdehaag, DeBilt, NETHERLANDS; Abraham Bout, Moerkapelle, NETHERLANDS;				
** CONTINUING DATA ***** THIS APPLN CLAIMS BENEFIT OF 60/129,452 04/15/1999				
** FOREIGN APPLICATIONS *****				
IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 07/05/2000				
** SMALL ENTITY **				
Foreign Priority claimed <input type="checkbox"/> yes <input type="checkbox"/> no 35 USC 119 (a-d) conditions <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> Met after met Allowance Verified and Acknowledged <u>Examiner's Signature</u> Initials		STATE OR COUNTRY NETHERLANDS	SHEETS DRAWING 27	TOTAL CLAIMS 71
INDEPENDENT CLAIMS 7				
ADDRESS Allen C Turner Trask Britt & Rossa P. O. Box 2550 Salt Lake City ,UT 84110				
TITLE Recombinant protein production in a human cell				
FILING FEE RECEIVED 2237	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit	

• Elected : Cl 1, 3, 5-7, 11, 13, 14

73-86, 97 and Influenza virus

09/549463

Claims

1. A method for producing at least one proteinaceous substance in a eukaryotic cell, said method comprising:

providing a eukaryotic cell having a nucleic acid sequence in the eukaryotic cell's genome, said nucleic acid sequence encoding at least one adenoviral E1 protein or a functional homologue, fragment or derivative thereof, which eukaryotic cell further does not encode a structural adenoviral protein in its genome or a sequence integrated therein;

providing said eukaryotic cell with a gene encoding a recombinant proteinaceous substance;

culturing said eukaryotic cell in a suitable medium; and

harvesting at least one proteinaceous substance from said eukaryotic cell, said suitable medium, or both said eukaryotic cell and said medium.

3. (Amended) The method according to claim 1 [or claim 2], wherein said eukaryotic cell is a mammalian cell.

5. (Twice amended) The method according to claim 1, wherein at least one of the proteinaceous substance harvested is encoded by said gene.

6. A method for producing at least one human recombinant protein in a cell, said method comprising:

providing a eukaryotic cell which is human, with a gene encoding a human recombinant protein, having a sequence encoding at least one adenoviral E1 protein or a functional derivative, homologue or fragment thereof in the human cell's genome which human cell further does not produce structural adenoviral proteins;

culturing said human cell in a suitable medium; and

harvesting the human recombinant protein from the human cell, the suitable medium, or both said human cell and said medium.

7. (Twice amended) The method according to claim 1, wherein said at least one adenoviral E1 protein comprises an E1A protein or a functional homologue, fragment and/or derivative thereof.

11. (Twice amended) The method according to claim 1, wherein said proteinaceous substance is a protein that undergoes post-translational and/or peri-translational modification.

13. (Twice amended) The method according to claim 1, wherein said proteinaceous substance is erythropoietin.

14. The method according to claim 13, wherein said eukaryotic cell produces in excess of 100 units erythropoietin thereof per million cells in 24 hours.

22. (Amended) A recombinant mammalian cell immortalized by the presence of at least one adenoviral E1A protein or a functional derivative, homologue and/or fragment thereof, said recombinant mammalian cell comprising:

a nucleic acid in a functional format for expressing at least one variable domain of an immunoglobulin or a functional derivative, homologue and/or fragment thereof; and
a nucleic acid derived from an adenovirus encoding said at least one E1A protein.

73. The method according to claim 6, wherein said human recombinant protein is a protein that undergoes post-translational and/or peri-translational modification.

74. The method according to claim 6, wherein said human recombinant protein is erythropoietin.

75. The method according to claim 74, wherein said eukaryotic cell produces in excess of 100 units erythropoietin thereof per million cells in 24 hours.

76. The method according to claim 1, wherein said eukaryotic cell is a human cell.

77. The method according to claim 1, wherein said proteinaceous substance comprises a viral protein other than an adenoviral protein.

78. The method according to claim 3, wherein said proteinaceous substance comprises a viral protein other than an adenoviral protein.

79. The method according to claim 11, wherein said proteinaceous substance comprises a viral protein other than an adenoviral protein.

80. The method according to claim 6, wherein said human recombinant protein comprises a viral protein other than an adenoviral protein.

81. The method according to claim 7, wherein said human recombinant protein comprises a viral protein other than an adenoviral protein.

82. The method according to claim 77, where said viral protein is selected from the group consisting of: an influenza virus neuramidase and/or a hemagglutinin; an enterovirus protein or a functional equivalent thereof; a herpes virus protein or a functional equivalent thereof; an orthomyxovirus protein; a retrovirus, a parvovirus or a popavovirus protein; a rotavirus or a coronavirus protein; a togavirus protein, rubella virus protein or an Eastern-, Western-, or Venezuelan equine encephalomyelitis virus protein; a hepatitis causing virus protein, a hepatitis A protein, or a hepatitis B virus protein; and a pestivirus protein, such as hog cholera virus protein or a rhabdovirus protein, such as a rabies virus protein.

83. The method according to claim 78, where said viral protein is selected from the group consisting of: an influenza virus neuramidase and/or a hemagglutinin; an enterovirus protein or a functional equivalent thereof; a herpes virus protein or a functional equivalent thereof; an orthomyxovirus protein; a retrovirus, a parvovirus or a popavovirus protein; a rotavirus or a coronavirus protein; a togavirus protein, rubella virus protein or an Eastern-, Western-, or Venezuelan equine encephalomyelitis virus protein; a hepatitis causing virus protein, a hepatitis A protein, or a hepatitis B virus protein; and a pestivirus protein, such as hog cholera virus protein or a rhabdovirus protein, such as a rabies virus protein.

84. The method according to claim 79, where said viral protein is selected from the group consisting of: an influenza virus neuramidase and/or a hemagglutinin; an enterovirus protein or a functional equivalent thereof; a herpes virus protein or a functional equivalent thereof; an orthomyxovirus

protein; a retrovirus, a parvovirus or a papovavirus protein; a rotavirus or a coronavirus protein; a togavirus protein, rubella virus protein or an Eastern-, Western-, or Venezuelan equine encephalomyelitis virus protein; a hepatitis causing virus protein, a hepatitis A protein, or a hepatitis B virus protein; and a pestivirus protein, such as hog cholera virus protein or a rhabdovirus protein, such as a rabies virus protein.

85. The method according to claim 80, where said viral protein is selected from the group consisting of: an influenza virus neuramidase and/or a hemagglutinin; an enterovirus protein or a functional equivalent thereof; a herpes virus protein or a functional equivalent thereof; an orthomyxovirus protein; a retrovirus, a parvovirus or a papovavirus protein; a rotavirus or a coronavirus protein; a togavirus protein, rubella virus protein or an Eastern-, Western-, or Venezuelan equine encephalomyelitis virus protein; a hepatitis causing virus protein, a hepatitis A protein, or a hepatitis B virus protein; and a pestivirus protein, such as hog cholera virus protein or a rhabdovirus protein, such as a rabies virus protein.

86. The method according to claim 81, where said viral protein is selected from the group consisting of: an influenza virus neuramidase and/or a hemagglutinin; an enterovirus protein or a functional equivalent thereof; a herpes virus protein or a functional equivalent thereof; an orthomyxovirus protein; a retrovirus, a parvovirus or a papovavirus protein; a rotavirus or a coronavirus protein; a togavirus protein, rubella virus protein or an Eastern-, Western-, or Venezuelan equine encephalomyelitis virus protein; a hepatitis causing virus protein, a hepatitis A protein, or a hepatitis B virus protein; and a pestivirus protein, such as hog cholera virus protein or a rhabdovirus protein, such as a rabies virus protein.

88. The method according to claim 1, wherein said eukaryotic cell further comprises a sequence encoding E2A or a functional derivative or analogue or fragment thereof in its genome.

89. The method according to claim 6, wherein said eukaryotic cell further comprises a sequence encoding E2A or a functional derivative or analogue or fragment thereof in its genome.

90. The method according to claim 88, wherein said E2A encoding sequence encodes a temperature sensitive mutant E2A.

91. The method according to claim 89, wherein said E2A encoding sequence encodes a temperature sensitive mutant E2A.

conclude
92. A recombinant erythropoietin molecule produced by the method of claim 1.

B6
93. A recombinant erythropoietin molecule produced by the method of claim 6.

94. The recombinant protein of claim 92 wherein said recombinant protein has a human glycosylation pattern different from that of the protein's isolated natural counterpart protein.

95. The recombinant protein of claim 93 wherein said recombinant protein has a human glycosylation pattern different from that of the protein's isolated natural counterpart protein.

96. The recombinant mammalian cell of claim 22, further comprising:
a nucleic acid derived from an adenovirus encoding an E1B protein.

97. The method according to claim 6, wherein said at least one adenoviral E1 protein comprises an E1A protein or a functional homologue, fragment and/or derivative thereof.

Abstract

Methods and compositions for the production of recombinant proteins in a human cell line. The methods and compositions are particularly useful for generating stable
5 expression of human recombinant proteins of interest that are modified post-translationally, for example, by glycosylation. Such proteins may have advantageous properties in comparison with their counterparts produced in non-human systems like Chinese Hamster Ovary cells.

=> fil capl

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L5 1 SEA FILE=REGISTRY ABB=ON ERYTHROPOIETIN/CN
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L7 5718 SEA FILE=CAPLUS ABB=ON (POSTTRANSLAT? OR PERITRANSLAT? OR
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L9 287 SEA FILE=CAPLUS ABB=ON L6(L)BPN/RL - Role BPN = Biosynthetic production
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L132 12 L10 OR L15 OR L19 OR L20 OR L23 OR L40

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=> d que l32; d que l35; d que l37

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L31 9799 SEA FILE=WPIDS ABB=ON E1#
L35 5 SEA FILE=WPIDS ABB=ON L28 AND L31 AND L30 AND D/DC

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L133 7 L32 OR L35 OR L37

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L49 3328 SEA FILE=BIOTECHNO ABB=ON ERYTHROPOIETIN/CT
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=> d que 197; d que 199

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L95 859032 SEA FILE=BIOSIS ABB=ON EXPRESS?
L96 194200 SEA FILE=BIOSIS ABB=ON RECOMBIN?
L97 2 SEA FILE=BIOSIS ABB=ON L84 AND L83 AND L87 AND (L95 OR L96)

L84 27163 SEA FILE=BIOSIS ABB=ON ADENOVIR?
L85 22979 SEA FILE=BIOSIS ABB=ON E1#
L88 15820 SEA FILE=BIOSIS ABB=ON ERYTHROPOIETIN#
L99 4 SEA FILE=BIOSIS ABB=ON L84 AND L85 AND L88

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L134 6 L97 OR L99

=> fil scisearch

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FILE COVERS 1974 TO 6 Sep 2002 (20020906/ED)

=> d que L115; d que L116; d que L130

L108 20683 SEA FILE=SCISEARCH ABB=ON ADENOVIR?
L109 18931 SEA FILE=SCISEARCH ABB=ON E1#
L111 13721 SEA FILE=SCISEARCH ABB=ON ERYTHROPOIETIN#
L115 4 SEA FILE=SCISEARCH ABB=ON L108 AND L109 AND L111

L108 20683 SEA FILE=SCISEARCH ABB=ON ADENOVIR?
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L112 53410 SEA FILE=SCISEARCH ABB=ON (EU!ARYOT? OR HUMAN OR MAMMAL?) (W)CE
LL#
L116 6 SEA FILE=SCISEARCH ABB=ON L108 AND L111 AND L112

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L112 53410 SEA FILE=SCISEARCH ABB=ON (EU!ARYOT? OR HUMAN OR MAMMAL?) (W)CE
LL#
L125 1467660 SEA FILE=SCISEARCH ABB=ON PRODUC? OR BIOSYN? OR MANUF?
L129 410 SEA FILE=SCISEARCH ABB=ON L110(5A);L125
L130 15 SEA FILE=SCISEARCH ABB=ON L129 AND L112

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L135 25 L115 OR L116 OR L130

=> dup rem L132,L51,L134,L135,L133

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PROCESSING COMPLETED FOR L133

L136 43 DUP REM L132 L51 L134 L135 L133 (11 DUPLICATES REMOVED)
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ANSWERS '13-15' FROM FILE BIOTECHNO

ANSWERS '16-19' FROM FILE BIOSIS
ANSWERS '20-40' FROM FILE SCISEARCH
ANSWERS '41-43' FROM FILE WPIDS

=> d ibib ab 1-43; fil hom

L136 ANSWER 1 OF 43 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:396521 CAPLUS
DOCUMENT NUMBER: 134:365703
TITLE: Production of viral proteins for use as vaccines from
immortalized mammalian cell lines
INVENTOR(S): Pau, Maria Grazia; Uytdehaag, Alphonsus Gerardus
Cornelis Maria
PATENT ASSIGNEE(S): Introgene B.V., Neth.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1103610	A1	20010530	EP 1999-203983	19991126
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2001038362	A2	20010531	WO 2000-NL862	20001124
WO 2001038362	A3	20020214		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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EP 1108787	A2	20010620	EP 2000-204190	20001124
EP 1108787	A3	20010829		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: EP 1999-203983 A 19991126

AB The invention relates to the field of prodn. of viruses and/or viral proteins other than adenovirus or adenoviral proteins for use as a vaccine to aid in protection against viral pathogens for vertebrates, in particular mammals and esp. human. Novel means and methods are provided for the prodn. of mammalian viruses, comprising infecting a culture of immortalized human cells with the virus, incubating the culture to propagate the virus under conditions that permit growth of the virus, and to form a virus-contg. medium, and removing the virus-contg. medium. Advantages - human cells can be cultured under defined serum free conditions. The preferred cell is derived from a human primary cell immortalized by a gene product of the adenoviral E1 gene, and said cell further comprises E2A gene. The invention discloses a novel human immortalized cell line (PER.C6) which was generated by transfection of primary human embryonic retinoblasts, using a plasmid that contained the Ad5 E1A and E1B genes under the control of the human phosphoglycerate kinase (PKG) promoter. In particular, methods are provided for producing in cultured human cells influenza virus and vaccines. This method eliminates the necessity to use whole chicken embryos for the prodn. of influenza vaccines. The method provides also for the continuous or batchwise removal of culture media, and as such, for large scale prodn. of viruses to a high titer.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 2 OF 43 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
 ACCESSION NUMBER: 2000:756885 CAPLUS
 DOCUMENT NUMBER: 133:318279
 TITLE: Manufacture of accurately processed proteins in human cell lines synthesizing adenovirus E1 and E2A tumor antigens
 INVENTOR(S): Hateboer, Guus; Verhulst, Karina Cornelia; Schouten, Govert Johan; Uytdehaag, Alphonsus Gerardus Cornelis Maria; Bout, Abraham
 PATENT ASSIGNEE(S): Introgene B.V., Neth.
 SOURCE: PCT Int. Appl., 127 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000063403	A2	20001026	WO 2000-NL247	20000417
WO 2000063403	A3	20010215		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1161548	A2	20011212	EP 2000-921175	20000417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001004977	A	20011217	NO 2001-4977	20011012
PRIORITY APPLN. INFO.:				
		EP 1999-201176	A	19990415
		EP 1999-204434	A	19991221
		WO 2000-NL247	W	20000417

AB Methods of manufg. foreign proteins with complete and accurate post-translational processing in human cell lines are described. Human cell lines have a .beta.-galactoside .alpha.2,6-sialyltransferase involved in sialylation that is absent from non-human mammalian cell lines. Cells are immortalized by transformation with the E1 and E2A genes of human **adenovirus**, but without the integration of other genes of **adenovirus**. Such proteins may have advantageous properties in comparison with their counterparts produced in non-human systems like Chinese Hamster Ovary (CHO) cells. The construction of a cell line carrying these antigen genes and the construction of an expression vector that used the cytomegalovirus immediate-early promoter and enhancer to express an erythropoietin gene is described. The cell lines that can grow in suspension or attached to a substrate and the copy no. of the gene can be increased by amplification of the segment using methotrexate and a dihydrofolate reductase marker. The manuf. of normally sialylated, biol. active human erythropoietin is demonstrated.

L136 ANSWER 3 OF 43 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4
 ACCESSION NUMBER: 1999:736960 CAPLUS
 DOCUMENT NUMBER: 131:347504
 TITLE: Improved multiviral compositions, and uses thereof for inducing rapamycin-dependent transcription of erythropoietin or growth hormone genes in mammals

INVENTOR(S): Wilson, James; Rivera, Victor; Gilman, Michael; Ye, Xuehai
PATENT ASSIGNEE(S): Ariad Gene Therapeutics, Inc., USA; University of Pennsylvania
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958700	A1	19991118	WO 1999-US10096	19990510
W: JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1078096	A1	20010228	EP 1999-922872	19990510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-76369 A 19980511
WO 1999-US10096 W 19990510

AB The invention provides a method for rendering a mammal capable of rapamycin-dependent transcription of an erythropoietin or growth hormone gene. The method involves infecting the mammal with two different recombinant viruses (adenoviruses, adeno-assocd. viruses, or hybrids thereof). One virus comprises an erythropoietin or growth factor gene operably linked to an IL-2 expression control sequence comprising twelve ZFHD1 binding sites. The other virus contains a bicistronic sequence encoding a ZFHD1-3/FKBP12 DNA-binding fusion protein and an FRB T2098L/p65 transcription activation fusion protein. Expression of erythropoietin or growth factor is induced within the transfected mammal by the administration of rapamycin.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 4 OF 43 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
ACCESSION NUMBER: 1999:723195 CAPLUS
DOCUMENT NUMBER: 131:318578
TITLE: Partially deleted adenoviral vectors with therapeutic expression potential for transgenes where deleted vector genes are introduced within producer cell chromosome

INVENTOR(S): Wadsworth, Samuel C.; Scaria, Abraham
PATENT ASSIGNEE(S): Genzyme Corp., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957296	A1	19991111	WO 1999-US9590	19990430
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2328087	AA	19991111	CA 1999-2328087	19990430
AU 9938770	A1	19991123	AU 1999-38770	19990430
EP 1075532	A1	20010214	EP 1999-921601	19990430
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

JP 2012513581 T2 20020514 JP 2000-847249 19990430
PRIORITY APPLN. INFO.: US 1998-93841P P 19980501
US 1999-118116P P 19990201
WO 1999-US9590 W 19990430

AB The invention is directed to novel partially deleted adenoviral vectors (DeAd) in which the majority of adenoviral early genes required for replication are deleted from the vector and placed within the chromosome of a producer cell line under conditional promoter control. Rephrased, the expression of genes encoding virion structural proteins is made conditional by replacement of the major late promoter with alternative promoters that can be controlled. Moreover, the procedures described here is directed to DeAd vectors in which expression of genes encoding virion structural proteins is diminished by deletion the VA RNA genes from the vector. This system is applicable to human adenovirus 2, 5, 6, and 17. The partially deleted adenoviral (DeAd) vectors of the invention can accommodate inserts, such as transgenes, of up to 12-15 kb in size. The invention is further directed to DeAd vector producer cell lines that contain the adenoviral early genes necessary for replication under conditional promoter control that allow for large scale prodn. of vectors. This conditional promoter system includes control sequences from the dimerizer gene or tetracycline or ecdysone control systems. The invention is also directed to methods for the prodn. of DeAd vectors in such cell lines and to the use of such vectors to deliver transgenes to target cells. These transgenes include the CFTR and human .alpha.-galactosidase A and erythropoietin and factor VII and factor IX.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 5 OF 43 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 1998:733603 CAPLUS
DOCUMENT NUMBER: 130:105805
TITLE: High-titer adeno-associated viral vectors from a Rep/Cap cell line and hybrid shuttle virus
AUTHOR(S): Gao, Guang-Ping; Qu, Guang; Faust, Lynn Z.; Engdahl, Ryan K.; Xiao, Weidong; Hughes, Joseph V.; Zoltick, Philip W.; Wilson, James M.
CORPORATE SOURCE: Institute for Human Gene Therapy, Department of Molecular and Cellular Engineering and Department of Medicine, University of Pennsylvania, Philadelphia, PA, 14104, USA
SOURCE: Human Gene Therapy (1998), 9(16), 2353-2362
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adeno-assocd. virus (AAV) is a potential vector for in vivo gene therapy. A crit. anal. of its utility has been hampered by methods of prodn. that are inefficient, difficult to scale up, and that often generate substantial quantities of replication-competent AAV. We describe a novel method for producing AAV that addresses these problems. A cell line, called B50, was created by stably transfecting into HeLa cells a rep/cap-contg. plasmid utilizing endogenous AAV promoters. Prodn. of AAV occurs in a two-step process. B50 is infected with an adenovirus defective in E2b, to induce Rep and Cap expression and provide helper functions, followed by a hybrid virus in which the AAV vector is cloned in the EI region of a replication-defective adenovirus. This results in a 100-fold amplification and rescue of the AAV genome, leading to a high yield of recombinant AAV that is free of replication-competent AAV. I.m. injection of vector encoding erythropoietin into skeletal muscle of mice resulted in supraphysiol. levels of hormone in serum that was sustained and caused polycythemia. This method of AAV prodn. should be useful in scaling up for studies in large animals, including humans.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 6 OF 43 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:505316 CAPLUS
DOCUMENT NUMBER: 137:74419
TITLE: Inducible eukaryotic expression system that regulates translation of proteins using aminoglycoside to suppress nonsense mutations in coding region
INVENTOR(S): Leiden, Jeffrey M.; Marshall, Deborah
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002086427	A1	20020704	US 2001-815980	20010322

PRIORITY APPLN. INFO.: US 2000-191568P P 20000323

AB A system for regulating the expression of a gene in a eukaryotic cell is provided, in which the expression of a desired gene can be activated or deactivated according to deliberate intentions (i.e., via an inducible signal) and in which regulation of gene expression occurs at the level of translation of the gene. This regulation is accomplished by, first, the introduction of at least one mutation into the coding sequence of the gene of interest. This mutation(s) causes a decrease or alteration of translation, and, hence, a decrease or alteration of expression of the desired gene. The method of the invention further involves contacting the eukaryotic cell contg. the now mutated gene of interest with an agent that is able to suppress the effect of the mutation, thus allowing translation, and, hence, expression of the desired gene. Preferably, the method involves introduction of a stop codon mutation, which is suppressed by an aminoglycoside. Nucleic acid compns. for use in the system of the invention, and kits for carrying out the methods of the invention, are also provided.

L136 ANSWER 7 OF 43 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:632708 CAPLUS
TITLE: Adeno-associated virus trans-splicing vectors with increased episomal stability and gene therapy applications
INVENTOR(S): Engelhardt, John F.; Duan, Dongsheng
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: U.S., 77 pp., Cont.-in-part of U.S. Provisional Ser. No. 86,166.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6436392	B1	20020820	US 1999-276625	19990325
CA 2328447	AA	19991125	CA 1999-2328447	19990520
WO 9906146	A1	19991125	WO 1999-US11197	19990520

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,

MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SE, UG, CN, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9941912 A1 19991206 AU 1999-40912 19990512
EP 1782444 A1 20010314 EP 1999-924404 19990520

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

JP 2002515257 T2 20020528 JP 2000-549752 19990520

PRIORITY APPLN. INFO.:

US 1998-86166P P 19980520
US 1999-276625 A 19990325
WO 1999-US11197 W 19990520

AB The invention provides an isolated and purified DNA mol. comprising at least one DNA segment, a biol. active subunit or variant thereof, of a circular intermediate of adeno-assocd. virus, which DNA segment confers increased episomal stability, persistence or abundance of the isolated DNA mol. in a host cell. The invention also provides a compn. comprising at least two adeno-assocd. virus vectors. This vector system has increased stability and/or persistence in host cells and is useful to express large open reading frames. The rAAV circular concatamers were used to delivery trans-splicing vectors with large gene inserts. Two rAAV vectors encoding two halves of a cDNA flanked by splice site consensus sequences are described. Full-length transgene mRNA is produced by splicing between these two vector-encoded sequences within circular concatamers. It was found that formation of head-to-tail circular AAV intermediates is augmented by superinfection with El-deleted **adenovirus** during transduction. Evidence for increased episomal persistence of AAV circular intermediate in model for in utero plasmid-based gene therapy was shown. Liposome mediated transfer of vectors to airway and muscle were successful. To prep. autonomously replicating circular episomes a rAAV vector comprising a replication origin of a circular episome is employed. For example, a rAAV vector comprising the EBV OriP and EBNA-1, the only viral protein needed to facilitate replication at this origin, was prepd. The **adenovirus** E2A protein is used to enhance episome stability. The CFTR, cystic fibrosis transmembrane conductance regulator protein, may be effectively expressed using this system and targeted to specific tissue. This vector system therefore can be used to manuf. a medicament to treat a pathol. condition in a mammal.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 8 OF 43 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:656017 CAPLUS

DOCUMENT NUMBER: 131:282377

TITLE: Engineering protein **posttranslational**
modification in transgenic non-human mammals

INVENTOR(S): Lubon, Henryk; Drohan, William N.; Paleyanda, Rekha K.

PATENT ASSIGNEE(S): American Red Cross, USA

SOURCE: U.S., 20 pp., Cont.-in-part of U.S. 5,589,604.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 8

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5965789	A	19991012	US 1995-434834	19950504
US 5831141	A	19981103	US 1992-943246	19920810
US 5559604	A	19961231	US 1994-247484	19940523
CA 2220109	AA	19961107	CA 1996-2220109	19960506
WO 9634966	A2	19961107	WO 1996-US6121	19960506

W: AU, CA, JP, MX

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9663474 A1 19961121 AU 1996-63474 19960506
JP 11509404 T2 19990824 JP 1996-533476 19960506
PRIORITY APPLN. INFO.: US 1991-638995 B1 19910111
US 1992-943246 A2 19920910
US 1994-198068 B1 19940208
US 1994-247484 A2 19940523
US 1995-434834 A 19950504
WO 1996-US6121 W 19960506

AB The invention relates to transgenic non-human multicellular organisms that contain polynucleotides for expressing proteins that alter posttranslational modification. In particular, the invention provides multiply-transgenic animals in which a first transgene encodes a first protein, a second transgene encodes a second protein, and expression of the second protein affects the posttranslational modification of the first protein in cells of said organism. Expression in preferred embodiments is in specific cells and the modified protein is secreted into a bodily fluid. An example provides transgenic mice which produce human protein C and the processing protease PACE/furin in mammary glands and secrete both proteins into milk. The protein C and furin genes are expressed from the mammary gland-specific promoter for whey acidic protein.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L136 ANSWER 9 OF 43 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:534522 CAPLUS

DOCUMENT NUMBER: 129:272001

TITLE: Structural characterization and independent folding of a chimeric glycoprotein comprising granulocyte-macrophage colony stimulating factor and erythropoietin sequences

AUTHOR(S): Amoresano, Angela; Andolfo, Annapaola; Siciliano, Rosa Anna; Mele, Antonio; Coscarella, Annamaria; De Santis, Rita; Mauro, Sandro; Pucci, Piero; Marino, Gennaro

CORPORATE SOURCE: Centro Internazionale di Servizi di Spettrometria di Massa, Naples, 80131, Italy

SOURCE: Glycobiology (1998), 8(8), 779-790

CODEN: GLYCE3; ISSN: 0959-6658

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB MEN 11300 is a hybrid glycoprotein of 297 amino acids obtained by fusion of the cDNA encoding GM-CSF with the cDNA encoding EPO followed by transfection of the hybrid gene into CHO cells. The oligonucleotide construct incorporated a spacing sequence between the two individual cDNAs which encodes eight amino acids constituting a linker peptide intended to sep. the GM-CSF and EPO moieties. The recombinant MEN 11300 protein was submitted to a detailed structural characterization including the verification of the entire amino acid sequence, the assignment of the disulfide bridges pattern, the identification of the glycosylation sites and the definition of the glycosidic moiety, including site-specificity. Partial processing of the C-terminal Arg residue and the occurrence of N-glycosylation sites at Asn27, Asn155, Asn169, Asn214 were established. Moreover, O-glycosylation at Ser257 and at the N-terminal region was also detected. A large heterogeneity was obsd. in the N-glycans due to the presence of differently sialylated and fucosylated branched complex type oligosaccharides whereas O-linked glycans were constituted by GalGalNAc chains with a different no. of sialic acids. The disulfide bridges pattern was established by direct FAB/MS anal. of the proteolytic digests or by ES/MS anal. of HPLC purified fractions. Pairing of the eight cysteine residues resulted in Cys54-Cys96, Cys88-Cys121, Cys138-Cys292, and Cys160-Cys164. This S-S bridges pattern is identical to that occurring in the individual natural GM-CSF and EPO, thus showing that the

two protein moieties in MEN 11300 can independently acquire their native three-dimensional structure.

L136 ANSWER 10 OF 43 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:6067 CAPLUS
DOCUMENT NUMBER: 126:27673
TITLE: Transgenic multicellular eukaryotes expressing genes
for enzymes of **post-translational**
modification of proteins
INVENTOR(S): Lubon, Henryk; Drohan, William N.; Paleyanda, Rekha K.
PATENT ASSIGNEE(S): American Red Cross, USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9634966	A2	19961107	WO 1996-US6121	19960506
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5965789	A	19991012	US 1995-434834	19950504
AU 9663474	A1	19961121	AU 1996-63474	19960506
JP 11509404	T2	19990824	JP 1996-533476	19960506
PRIORITY APPLN. INFO.:				
US 1995-434834 A 19950504				
US 1991-638995 B1 19910111				
US 1992-943246 A2 19920910				
US 1994-198068 B1 19940208				
US 1994-247484 A2 19940523				
WO 1996-US6121 W 19960506				

AB Transgenic non-human multicellular organisms contg. expression cassettes for enzyme involved in post-translational modification of proteins are described for use in the manuf. of proteins. The transgenic organism most often carries genes for enzymes of post-translational modification and the gene for a protein of interest that is a substrate for the modification enzyme. Preferably, the genes are regulated, e.g. by development, tissue-type, or by a chem. inducer and the modified protein is secreted into a bodily fluid. An example provides transgenic mice that synthesize human protein C and the processing protease PACE/furin in mammary glands and secrete both proteins into milk. The genes are placed under control of the mammary gland-specific promoter of the whey acidic protein gene.

L136 ANSWER 11 OF 43 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1996:433122 CAPLUS
DOCUMENT NUMBER: 125:134213
TITLE: Interaction cloning of NS1-I, a human protein that binds to the nonstructural NS1 proteins of influenza A and B viruses
AUTHOR(S): Wolff, Thorsten; O'Neill, Robert E.; Palese, Peter
CORPORATE SOURCE: Dep. Microbiology, Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Journal of Virology (1996), 70(8), 5363-5372
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The yeast interaction trap system was used to identify NS1-I (for NS1 interactor), which is a human protein that binds to the nonstructural NS1 protein of the influenza A virus. NS1-I is a human homolog of the porcine 17.beta.-estradiol dehydrogenase precursor protein, to which it is 84% identical. We detected only one NS1-I mRNA species, of about 3.0 kb, in

HeLa cells, and the NS1-I cDNA was found to have a coding capacity for a 79.6-kDa protein. However, immunoblot anal. detected predominantly a 55-kDa protein in human cells, suggesting that NS1-I, like the porcine 17.beta.-estradiol dehydrogenase, is posttranslationally processed. Using an in vitro copptn. assay, we showed that NS1-I interacts with NS1 proteins from exts. of cells infected with five different influenza A virus strains as well as with the NS1 of an influenza B virus. The fact that influenza A and influenza B virus NS1 proteins bind to NS1-I suggests that this cellular protein plays a role in the influenza virus life cycle.

L136 ANSWER 12 OF 43 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:566280 CAPLUS
DOCUMENT NUMBER: 105:166280
TITLE: Vectors containing accessory dna for transformation of
eukaryotic cells
PATENT ASSIGNEE(S): Genetics Institute, Inc., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 41 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 61012288	A2	19860120	JP 1984-281862	19841227
JP 2648301	B2	19970827		
US 4740461	A	19880426	US 1983-566057	19831227
DK 8406107	A	19850816	DK 1984-6107	19841219
AU 8437051	A1	19860626	AU 1984-37051	19841221
ZA 8410034	A	19860827	ZA 1984-10034	19841221
JP 09107978	A2	19970428	JP 1996-215721	19841227
JP 10052266	A2	19980224	JP 1997-142690	19841227
ZA 8508962	A	19860730	ZA 1985-8962	19851122
AT 71408	E	19920115	AT 1990-118215	19851203
US 5079159	A	19920107	US 1988-185649	19880425
JP 06189758	A2	19940712	JP 1993-256173	19931013
LT 3944	B	19960527	LT 1993-1481	19931125

PRIORITY APPLN. INFO.:
US 1983-565627 A 19831227
US 1983-566057 A 19831227
US 1984-677813 A 19841204
US 1985-688622 A 19850103
US 1985-693258 A 19850122
EP 1990-118215 A 19851203
JP 1993-256173 A3 19931013

AB Recombinant vectors are prepd., that are capable of directing the synthesis of a heterologous protein in eukaryotic cells. Thus, a DNA fragment (RKFL13) was constructed with the small EcoRI DNA fragment contg. erythropoietin gene of clone .lambda. HEPOFL13 under the regulation of the **adenovirus** promoters and transcriptional and translational activating sequences of recombinant plasmid pRK1-4. RKFL13 was microinjected into dihydrofolic reductase-deficient CHO cells to give DEPO-1. DEPO-1 produced erythropoietin (160 mg/mL) in a medium contg. 0.02 .mu.M methotrexate.

L136 ANSWER 13 OF 43 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.DUPLICATE
ACCESSION NUMBER: 1996:26424249 BIOTECHNO
TITLE: Gene delivery to skeletal muscle results in sustained expression and systemic delivery of a therapeutic protein
AUTHOR: Kessler P.D.; Podsakoff G.M.; Chen X.; McQuiston S.A.; Colosi P.C.; Matelis L.A.; Kurtzman G.J.; Byrne B.J.
CORPORATE SOURCE: G.J. Kurtzman, Peter Beller Cardiac Laboratory, Johns

SOURCE: Hopkins Univ. Sch. of Medicine, 720 Rutland Avenue,
Baltimore, MD 21205, United States.
Proceedings of the National Academy of Sciences of the
United States of America, (1996), 93/24 (14062-14067)
CODEN: PNASA6 ISSN: 0027-8424

DOCUMENT TYPE: Journal; Conference Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Somatic gene therapy has been proposed as a means to achieve systemic delivery of therapeutic proteins. However, there is limited evidence that current methods of gene delivery can practically achieve this goal. In this study, we demonstrate that, following a single intramuscular administration of a recombinant adeno-associated virus (rAAV) vector containing the .beta.-galactosidase (AAV-lacZ) gene into adult BALB/c mice, protein expression was detected in myofibers for at least 32 weeks. A single intramuscular administration of an AAV vector containing a gene for human erythropoietin (AAV-Epo) into mice resulted in dose-dependent secretion of erythropoietin and corresponding increases in red blood cell production that persisted for up to 40 weeks. Primary human myotubes transduced in vitro with the AAV-Epo vector also showed dose-dependent production of Epo. These results demonstrate that rAAV vectors are able to transduce skeletal muscle and are capable of achieving sustained expression and systemic delivery of a therapeutic protein following a single intramuscular administration. Gene therapy using AAV vectors may provide a practical strategy for the treatment of inherited and acquired protein deficiencies.

L136 ANSWER 14 OF 43 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.DUPLICATE

ACCESSION NUMBER: 1994:24328083 BIOTECHNO

TITLE: Stimulation of erythropoiesis by in vivo gene therapy:
Physiologic consequences of transfer of the human
erythropoietin gene to experimental animals using an
adenovirus vector

AUTHOR: Setoguchi Y.; Danel C.; Crystal R.G.

CORPORATE SOURCE: Div. of Pulmonary/Critical Care Med., New York
Hosp.-Cornell Medical Ctr., 520 E 70th St, New York, NY
10021, United States.

SOURCE: Blood, (1994), 84/9 (2946-2953)
CODEN: BLOOAW ISSN: 0006-4971

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Erythropoietin (Epo), a 30.4-kD glycoprotein, is the principal regulator of erythropoiesis. To evaluate the concept that in vivo gene transfer might be used as an alternative to recombinant human Epo (rhEpo) in applications requiring a 1- to 3-week stimulation of erythropoiesis, the replication-deficient recombinant **adenovirus** AdMLP.Epo was constructed by deleting the majority of E1 from **adenovirus** type 5, and replacing E1 with an expression cassette containing the **adenovirus** type 5 major late promoter (MLP) and the human Epo gene, including the 3' cis-acting hypoxia response element. In vitro studies showed that infection of the human hepatocyte cell line Hep3B with AdMLP.Epo resulted in a 15-fold increase in Epo production in 24 hours that was enhanced to 116-fold in the presence of a hypoxic stimulus. One-time in vivo administration of AdMLP.Epo (7×10^8 sup.9 plaque-forming units/kg) to the peritoneum of cotton rats caused a marked increase in red blood cell production, with a 2.6-fold increase in bone marrow erythroid precursors by day 4, and sevenfold increase in reticulocyte count by day 7. The hematocrit increased gradually, with a maximum of $64 \pm 4\%$ at day 14 (compared with an untreated baseline of $46 \pm 2\%$), and a level of $55 \pm 1\%$ at day 24. Furthermore, one-time

subcutaneous administration of AdMLP.Epo caused an increase in hematocrit that peaked at 14 days (57% \pm 2%) and was still elevated at day 42. Hematocrit level in animals receiving subcutaneous administration of AdMLP.Epo sustained a long-term increase compared with animals receiving intra-peritoneal administration. In the context of these observations, gene therapy with a single administration of an **adenovirus** vector containing the human EPO gene may provide a means of significantly augmenting the circulating red blood cell mass over the 1- to 3-week period necessary for many clinical applications.

L136 ANSWER 15 OF 43 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.
ACCESSION NUMBER: 2001:32747574 BIOTECHNO
TITLE: A hypoxia-regulated adeno-associated virus vector for cancer-specific gene therapy
AUTHOR: Ruan H.; Su H.; Hu L.; Lamborn K.R.; Kan Y.W.; Deen D.F.
CORPORATE SOURCE: Dr. D.F. Deen, Brain Tumor Research Center, University of California, San Francisco, CA 94143-0520, United States.
E-mail: ddeen@itsa.ucsf.edu
SOURCE: Neoplasia, (2001), 3/3 (255-263), 35 reference(s)
CODEN: NEOPFL ISSN: 1522-8002
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The presence of hypoxic cells in human brain tumors is an important factor leading to resistance to radiation therapy. However, this physiological difference between normal tissues and tumors also provides the potential for designing cancer-specific gene therapy. We compared the increase of gene expression under anoxia (<0.01% oxygen) produced by 3, 6, and 9 copies of hypoxia-responsive elements (HRE) from the erythropoietin gene (Epo), which are activated through the transcriptional complex hypoxia-inducible factor 1 (HIF-1). Under anoxic conditions, nine copies of HRE (9XHRE) yielded 27- to 37-fold of increased gene expression in U-251 MG and U-87 MG human brain tumor cell lines. Under the less hypoxic conditions of 0.3% and 1% oxygen, gene activation by 9XHRE increased expression 11- to 18-fold in these cell lines. To generate a recombinant adeno-associated virus (rAAV) in which the transgene can be regulated by hypoxia, we inserted the DNA fragment containing 9XHRE and the LacZ reporter gene into an AAV vector. Under anoxic conditions, this vector produced 79- to 110-fold increase in gene expression. We believe this hypoxia-regulated rAAV vector will provide a useful delivery vehicle for cancer-specific gene therapy.

L136 ANSWER 16 OF 43 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
ACCESSION NUMBER: 2001:334834 BIOSIS
DOCUMENT NUMBER: PREV200100334834
TITLE: Biology of **E1-deleted adenovirus** vectors in nonhuman primate muscle.
AUTHOR(S): Zoltick, Philip W.; Chirmule, Narendra; Schnell, Michael A.; Gao, Guang-Ping; Hughes, Joseph V.; Wilson, James M.
(1)
CORPORATE SOURCE: (1) 204 Wistar Institute, 3601 Spruce Street, Philadelphia, PA, 19104-4268: wilsonjm@mail.med.upenn.edu USA
SOURCE: Journal of Virology, (June, 2001) Vol. 75, No. 11, pp. 5222-5229. print.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Adenovirus** vectors have been studied as vehicles for gene

transfer to skeletal muscle, an attractive target for gene therapies for inherited and acquired diseases. In this setting, immune responses to viral proteins and/or transgene products cause inflammation and lead to loss of transgene expression. A few studies in murine models have suggested that the destructive cell-mediated immune response to virally encoded proteins of **E1-deleted adenovirus** may not contribute to the elimination of transgene-expressing cells. However, the impact of immune responses following intramuscular administration of **adenovirus** vectors on transgene stability has not been elucidated in larger animal models such as nonhuman primates. Here we demonstrate that intramuscular administration of **E1-deleted adenovirus** vector expressing rhesus monkey **erythropoietin** or growth hormone to rhesus monkeys results in generation of a Th1-dependent cytotoxic T-cell response to **adenovirus** proteins. Transgene expression dropped significantly over time but was still detectable in some animals after 6 months. Systemic levels of **adenovirus**-specific neutralizing antibodies were generated, which blocked vector readministration. These studies indicate that the cellular and humoral immune response generated to **adenovirus** proteins, in the context of transgenes encoding self-proteins, hinders long-term transgene expression and readministration with first-generation vectors.

L136 ANSWER 17 OF 43 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

7

ACCESSION NUMBER: 1997:131632 BIOSIS

DOCUMENT NUMBER: PREV199799423445

TITLE: **Erythropoietin** gene regulation depends on heme-dependent oxygen sensing and assembly of interacting transcription factors.

AUTHOR(S): Huang, L. Eric; Ho, Vincent; Arany, Zoltan; Krainc, Dimitri; Galson, Deborah; Tendler, Drory; Livingston, David M.; Bunn, H. Franklin (1)

CORPORATE SOURCE: (1) Hematol. Oncol. Div., Brigham and Women's Hosp., Longwood Med. Res. Cent., 221 Longwood Ave., Room 223, Boston, MA USA

SOURCE: Kidney International, (1997) Vol. 51, No. 2, pp. 548-552. ISSN: 0085-2538.

DOCUMENT TYPE: Journal; Article

LANGUAGE: English

AB Studies on **erythropoietin** (Epo) gene expression have been useful in investigating the mechanism by which cells and tissues sense hypoxia. Both in vivo and in Hep3B cells, Epo production is induced not only by hypoxia but also by certain transition metals (cobalt and nickel) and by iron chelation. When Hep3B cells were incubated in an iron deficient medium, Epo mRNA expression was enhanced fourfold compared to Hep3B cells in iron enriched medium. Epo induction by cobalt was inversely related to iron concentration in the medium, indicating competition between the two metals. Under hyperbaric oxygen, cobalt induction of **erythropoietin** mRNA was modestly suppressed while nickel induction was markedly enhanced. These recent observations support the proposal that the oxygen sensor is a heme protein in which cobalt and nickel can substitute for iron in the porphyrin ring. The up-regulation of Epo gene transcription by hypoxia depends on at least two known DNA binding transcription factors, HIF-1 and HNF-4, which bind to cognate response elements in a critical approx 50 bp 3' enhancer. Hypoxia induces HIF-1 binding. HNF-4, an orphan nuclear receptor constitutively expressed in kidney and liver, binds downstream of HIF-1 and cooperates with HIF-1, contributing importantly to high level and perhaps tissue specific expression. The C-terminal activation domain of HNF-4 binds to the beta subunit of HIF-1. The C-terminal portion of the alpha subunit of HIF-1 binds specifically to p300, a general transcriptional activator. Hypoxic induction of the endogenous Epo gene in Hep3B cells as well as an Epo-reporter gene was fully inhibited by **E1A**, an

adenovirus protein that binds to and inactivates p300, but only slightly by a mutant **E1A** that fails to bind to p300. Moreover, overexpression of p300 enhanced hypoxic induction. Thus, it is likely that in hypoxic cells, p300 or a related family member plays a critical role in forming a macromolecular assembly with HIF-1 and HNF-4, enabling transduction from the Epo 3' enhancer to the apparatus on the promoter responsible for the initiation of transcription.

L136 ANSWER 18 OF 43 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:155388 BIOSIS

DOCUMENT NUMBER: PREV199344074188

TITLE: Transferrinfection: A highly efficient way to
express gene constructs in **eukaryotic**
cells.

AUTHOR(S): Zatloukal, Kurt (1); Wagner, Ernst (1); Cotten, Matt (1);
Phillips, Stephen (1); Plank, Christina (1); Steinlein,
Peter (1); T. curiel, David; Birnstiel, Max L. (1)

CORPORATE SOURCE: (1) Res. Inst. Moelcualr Pathol., Dr. Bohr-Gasse 7, A-1030
Vienna Austria

SOURCE: Baserga, R. [Editor]; Denhardt, D. T. [Editor]. Annals of
the New York Academy of Sciences, (1992) Vol. 660, pp.
136-153. Annals of the New York Academy of Sciences;
Antisense strategies.
Publisher: New York Academy of Sciences 2 East 63rd Street,
New York, New York 10021, USA.
Meeting Info.: Conference Philadelphia, Pennsylvania, USA
January 12-15, 1992
ISSN: 0077-8923. ISBN: 0-89766-748-4 (paper), 0-89766-747-6
(cloth).

DOCUMENT TYPE: Article

LANGUAGE: English

L136 ANSWER 19 OF 43 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1989:354724 BIOSIS

DOCUMENT NUMBER: BA88:46838

TITLE: COMPARATIVE SUSCEPTIBILITY OF RESPIRATORY VIRUSES TO
RECOMBINANT INTERFERONS-ALPHA-2B AND BETA.

AUTHOR(S): SPERBER S J; HAYDEN F G

CORPORATE SOURCE: DEP. INTERNAL MED., UNIV. VA. MED. CENT., BOX 437,
CHARLOTTESVILLE, VA. 22908.

SOURCE: J INTERFERON RES, (1989) 9 (3), 285-294.
CODEN: JIREDJ. ISSN: 0197-8357.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB Intranasal **recombinant** interferon-.alpha.2b (rIFN-.alpha.2b)
protects against natural colds due to rhinoviruses, but apparently not
against those caused by viruses. Because rIFN-.beta.serinel7
(rIFN-.beta.ser) appears less active than rIFN-.alpha.2b in preventing
natural rhinovirus colds, we compared the two IFNs in two in vitro assays
against selected respiratory viruses. In a yield reduction assay, both
IFNs had comparable activity against rhinovirus types 39 and 1A and
coronavirus 229E, which were inhibited by 90% or more at IFN
concentrations of 10⁻¹¹ to 10⁻¹⁰ gram of protein/ml (approximately 2-20
IU/ml). Similar activities were observed with rIFN-.beta.ser against
rhinoviruses isolated from clinical specimens. At concentrations of 10⁻⁹
gram protein/ml, both IFNs inhibited the growth of **influenza A**
and parainfluenza viruses, but not of **adenovirus** or respiratory
syncytial virus in the cell culture systems tested. Thus, the different
clinical protection conferred by rIFN-.alpha.2b and rIFN-.beta.ser in
studies of natural rhinovirus colds are not accounted for by differences
in their in vitro activity against these viruses, and other explanations
must be found.

L136 ANSWER 20 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:641982 SCISEARCH
THE GENUINE ARTICLE: 577DG
TITLE: Human influenza viruses activate an interferon-independent transcription of cellular antiviral genes: Outcome with influenza A virus is unique
AUTHOR: Kim M J; Latham A G; Krug R M (Reprint)
CORPORATE SOURCE: Univ Texas, Inst Cellular & Mol Biol, Sect Mol Genet & Microbiol, Austin, TX 78712 USA (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (23 JUL 2002) Vol. 99, No. 15, pp. 10096-10101.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
ISSN: 0027-8424.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 46

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We examine the IFN-alpha/beta-independent activation of cellular transcription that constitutes an early antiviral response of cells against influenza A and B viruses, which cause widespread epidemics in humans. We show that influenza B virus induces the synthesis in **human cells** of several mature mRNAs encoded by genes containing an IFN-alpha/beta-stimulated response element (ISRE). Consequently, the IFN regulatory factor-3 transcription factor, which is required for the transcription of ISRE-controlled genes, is activated after **influenza B** virus infection. The **production** of these cellular mRNAs, some of which encode antiviral proteins, is independent of not only IFN-alpha/beta, but also viral protein synthesis. These mature cellular antiviral mRNAs are not **produced** after infection with **influenza A** virus, but IFN regulatory factor-3 is activated and the transcription of the ISRE-controlled p56 gene is induced. Consequently, like other newly synthesized cellular premRNAs in influenza A virus infected cells, the posttranscriptional processing of premRNAs encoded by ISRE-controlled genes is inhibited. Previous work has established that such posttranscriptional inhibition is mediated by the viral NS1A protein. This unique, global countermeasure against the early, IFN-alpha/beta-independent antiviral response of cells may be an important factor in the pathogenicity of influenza A virus infection.

L136 ANSWER 21 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2002:176316 SCISEARCH
THE GENUINE ARTICLE: 521TV
TITLE: Safety and immunogenicity of a trivalent, inactivated, **mammalian cell** culture-derived influenza vaccine in healthy adults, seniors, and children
AUTHOR: Halperin S A (Reprint); Smith B; Mabrouk T; Germain M; Trepanier P; Hassell T; Treanor J; Gauthier R; Mills E L
CORPORATE SOURCE: Dalhousie Univ, Clin Trials Res Ctr, IWK Hlth Ctr, Dept Pediat, 5850 Univ Ave, Halifax, NS B3J 3G9, Canada (Reprint); Dalhousie Univ, Clin Trials Res Ctr, IWK Hlth Ctr, Dept Pediat, Halifax, NS B3J 3G9, Canada; Dalhousie Univ, Clin Trials Res Ctr, IWK Hlth Ctr, Dept Microbiol & Immunol, Halifax, NS B3J 3G9, Canada; Dalhousie Univ, Dept Math, Halifax, NS B3J 3G9, Canada; Dalhousie Univ, Dept Stat, Halifax, NS B3J 3G9, Canada; BioChem Pharma, Laval, PQ, Canada; Univ Rochester, Dept Med, Rochester, NY USA; Hop Maisson Neuve Rosemont, Montreal, PQ H1T 2M4, Canada; McGill Univ, Laval, PQ, Canada
COUNTRY OF AUTHOR: Canada; USA
SOURCE: VACCINE, (15 JAN 2002) Vol. 20, No. 7-8, pp. 1240-1247.

Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE,
KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.

ISSN: 0264-410X.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We performed randomized, double-blind, controlled trials to assess the safety and immunogenicity of an inactivated, Madin Darby Canine Kidney (MDCK)-derived cell line **produced influenza** vaccine in healthy adults (19-50 years), children (3-12 years) and the elderly (greater than or equal to 65 years). We studied three lots of cell culture-derived vaccine and one lot of licensed egg-derived vaccine in healthy adults (n = 462), two lots of cell culture-derived vaccine and one lot of egg-derived vaccine in seniors (n = 269), and one lot of each vaccine in children (n = 209). Adverse events were collected during the first 3 days post-immunization; serum was collected before and 1 month after immunization. Rates of local and system adverse reactions were similar with both vaccines. An injection site adverse event rated at least moderate severity was reported by 21.9% of children who received the egg-derived vaccine and 25.0% of those who received the cell culture-derived vaccine. In healthy adults the proportions were 12.1 and 15.3%, respectively and 6.7 and 6.3%, respectively in seniors. Systemic events of at least moderate severity were 12.4 and 12.5% in children, 19.8 and 13.6% in healthy adults, and 14.1 and 9.7% in seniors; none of these differences were statistically significant. The antibody response against all three viruses was similar between the two vaccines. From 83 to 100% of children, healthy adults and seniors achieved hemagglutination inhibition titers in excess of 40 post-immunization. We conclude that the cell culture-derived vaccine was safe and immunogenic in children, healthy adults and seniors. (C) 2002 Elsevier Science Ltd. All rights reserved.

L136 ANSWER 22 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2001:412709 SCISEARCH

THE GENUINE ARTICLE: 4300J

TITLE: Sequences in influenza A virus PB2 protein that determine **productive** infection for an avian **influenza** virus in mouse and **human** cell lines

AUTHOR: Yao Y X; Mingay L J; McCauley J W; Barclay W S (Reprint)
CORPORATE SOURCE: Univ Reading, Sch Anim & Microbial Sci, POB 228, Reading RG6 6AJ, Berks, England (Reprint); Univ Reading, Sch Anim & Microbial Sci, Reading RG6 6AJ, Berks, England; Univ Oxford, Sir William Dunn Sch Pathol, Oxford OX1 3RE, England; Inst Anim Hlth, Compton Lab, Newbury RG20 7NN, Berks, England

COUNTRY OF AUTHOR: England

SOURCE: JOURNAL OF VIROLOGY, (JUN 2001) Vol. 75, No. 11, pp. 5410-5415.

Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW,
WASHINGTON, DC 20036-2904 USA.

ISSN: 0022-538X.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Reverse genetics was used to analyze the host range of two avian influenza viruses which differ in their ability to replicate in mouse and **human cells** in culture, Engineered viruses carrying sequences encoding amino acids 362 to 581 of PB2 from a host range variant productively infect mouse and **human cells**.

L136 ANSWER 23 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2001:492677 SCISEARCH
THE GENUINE ARTICLE: 437LF
TITLE: Comparison of large-scale **mammalian cell**
culture systems with egg culture for the
production of influenza virus A vaccine
strains
AUTHOR: Tree J A (Reprint); Richardson C; Fooks A R; Clegg J C;
Looby D
CORPORATE SOURCE: CAMR, Salisbury SP4 0JG, Wilts, England (Reprint); Univ
Greenwich, London W1 4DJ, England
COUNTRY OF AUTHOR: England
SOURCE: VACCINE, (14 MAY 2001) Vol. 19, No. 25-26, pp. 3444-3450.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE,
KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 0264-410X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Different types of microcarriers were assessed for the large-scale
culture of influenza virus in the Madin-Darby canine kidney (MDCK) cells.
Both porous and solid carriers were examined. A higher titre of influenza
A/PR8/34 virus was recovered from cultures using solid (1.3×10^9 PFU
per ml) rather than porous carriers (4.0×10^8 PFU per ml). High titres
of virus (1.0×10^9 PFU per ml) were also obtained from roller bottle
cultures of MDCK cells and the traditional culture technique using
embryonated hens eggs (3.9×10^9 PFU per ml). We found that solid
carriers composed of dextran with a positive charge are the most suitable
carriers for the large-scale growth of influenza A virus in MDCK cells
using serum-free media. Groan Copyright (C) 2001 Published by Elsevier
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L136 ANSWER 24 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2001:274001 SCISEARCH
THE GENUINE ARTICLE: 412DH
TITLE: The **human cell** line PER.C6 provides a
new **manufacturing** system for the
production of influenza vaccines
AUTHOR: Pau M G (Reprint); Ophorst C; Koldijk M H; Schouten G;
Mehtali M; Uytdehaag F
CORPORATE SOURCE: IntroGene BV, Crucell Holland BV, Archimedesweg 4, NL-2333
CN Leiden, Netherlands (Reprint); IntroGene BV, Crucell
Holland BV, NL-2333 CN Leiden, Netherlands
COUNTRY OF AUTHOR: Netherlands
SOURCE: VACCINE, (21 MAR 2001) Vol. 19, No. 17-19, Sp. iss. SI,
pp. 2716-2721.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE,
KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 0264-410X.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 9

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Influenza** viruses for vaccine **production** are
currently grown on embryonated eggs. This manufacturing system conveys
many major drawbacks such as inflexibility, cumbersome down stream
processing, inability of some strains to replicate on eggs to high enough
yields, and selection of receptor-binding variants with reduced
antigenicity. These limitations emphasize the need for a cell line-based
production system that could replace eggs in the **production of**
influenza virus vaccines in a pandemic proof fashion. Here we
present the efficient propagation of influenza A and B viruses on the
fully characterized and standardized **human cell** line

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L136 ANSWER 25 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:665446 SCISEARCH
THE GENUINE ARTICLE: 347ML
TITLE: Effect of the cytoplasmic domain of the simian immunodeficiency virus envelope protein on incorporation of heterologous envelope proteins and sensitivity to neutralization
AUTHOR: Vzorov A N; Compans R W (Reprint)
CORPORATE SOURCE: EMORY UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, ATLANTA, GA 30322 (Reprint); EMORY UNIV, SCH MED, DEPT MICROBIOL & IMMUNOL, ATLANTA, GA 30322; EMORY UNIV, SCH MED, EMORY VACCINE CTR, ATLANTA, GA 30322
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF VIROLOGY, (SEP 2000) Vol. 74, No. 18, pp. 8219-8225.
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904.
ISSN: 0022-538X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In addition to the viral envelope (Env) proteins, host cell-derived proteins have been reported to be present in human immunodeficiency virus and simian immunodeficiency virus (SIV) envelopes, and it has been postulated that they may play a role in infection. We investigated whether the incorporation of host cell proteins is affected by the structure and level of incorporation of viral Env proteins. To compare the cellular components incorporated into STV particles and how this is influenced by the structure of the cytoplasmic domain, we compared SIV virions with full-length and truncated Env proteins. The levels of HLA-I and HLA-II molecules were found to be significantly (15- to 25-fold) higher in virions with full-length Env than in those with a truncated Env. Virions with a truncated Env were also found to be less susceptible to neutralization by specific antibodies against HLA-I or HLA-II proteins. We also compared the level of incorporation into SIV virions of a coexpressed heterologous viral glycoprotein, the influenza virus hemagglutinin (HA) protein. We found that SIV infection of cells expressing **influenza virus HA** resulted in the **production** of phenotypically mixed SIV virions containing influenza virus HA as well as SIV envelope proteins. The HA proteins were more effectively incorporated into virions with full-length Env than in virions with truncated Env. The phenotypically mixed particles, with full-length Env, containing higher levels of HA, were sensitive to neutralization with anti-HA antibody, whereas virions with truncated Env proteins and containing lower levels of HA were more resistant to neutralization by anti-HA antibody. In contrast, SIV virions with truncated Env proteins were found to be highly sensitive to neutralization by antisera to SIV, whereas virions with full-length Env proteins were relatively resistant to neutralization. These results indicate that the cytoplasmic domain of SIV Env affects the incorporation of cellular as well as heterologous viral membrane proteins into the SIV envelope and may be an important determinant of the sensitivity of the virus to neutralizing antibodies.

L136 ANSWER 26 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:90302 SCISEARCH
THE GENUINE ARTICLE: 277XC
TITLE: Role of the influenza virus M1 protein in nuclear export of viral ribonucleoproteins
AUTHOR: Bui M; Wills E G; Helenius A; Whittaker G R (Reprint)

CORPORATE SOURCE: CORNELL UNIV, VET MED CTR C6141, DEPT MICROBIOL & IMMUNOL, ITHACA, NY 14853 (Reprint); CORNELL UNIV, VET MED CTR C6141, DEPT MICROBIOL & IMMUNOL, ITHACA, NY 14853; YALE UNIV, SCH MED, DEPT CELL BIOL, NEW HAVEN, CT 06510

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF VIROLOGY, (FEB 2000) Vol. 74, No. 4, pp. 1781-1786.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0022-538X.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The protein kinase inhibitor H7 blocks **influenza** virus replication, inhibits **production** of the matrix protein (M1), and leads to a retention of the viral ribonucleoproteins (vRNPs) in the nucleus at late times of infection (K. Martin and A. Helenius, Cell 67:117-130, 1991). We show here that production of assembled vRNPs occurs normally in H7-treated cells, and we have used H7 as a biochemical tool to trap vRNPs in the nucleus. When H7 was removed from the cells, vRNP export was specifically induced in a CHO cell line stably expressing recombinant M1. Similarly, fusion of cells expressing recombinant M1 from a Semliki Forest virus vector allowed nuclear export of vRNPs. However, export was not rescued when H7 was present in the cells, implying an additional role for phosphorylation in this process. The viral NS2 protein was undetectable in these systems. We conclude that influenza virus M1 is required to induce vRNP nuclear export but that cellular phosphorylation is an additional factor.

L136 ANSWER 27 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:361307 SCISEARCH

THE GENUINE ARTICLE: 311UR

TITLE: Regulatable systems: applications in gene therapy and replicating viruses

AUTHOR: AghaMohammadi S (Reprint); Lotze M T

CORPORATE SOURCE: UNIV PITTSBURGH, CTR MED, W1543 BIOMED SCI TOWER, LOTHROP ST, PITTSBURGH, PA 15261 (Reprint)

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (MAY 2000) Vol. 105, No. 9, pp. 1177-1183.
Publisher: AMER SOC CLINICAL INVESTIGATION INC, ROOM 4570 KRESGE I, 200 ZINA PITCHER PLACE, ANN ARBOR, MI 48109-0560

ISSN: 0021-9738.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 43

L136 ANSWER 28 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2001:30308 SCISEARCH

THE GENUINE ARTICLE: 383QW

TITLE: Humoral and cell-mediated immunity to Vero cell-derived influenza vaccine

AUTHOR: Bruhl P; Kerschbaum A; Kistner O; Barrett N; Dorner F; Gerencer M (Reprint)

CORPORATE SOURCE: Baxter Hyland Immuno, Dept Cellular Immunol, Ind Str 131, A-1221 Vienna, Austria (Reprint); Baxter Hyland Immuno, Dept Cellular Immunol, A-1221 Vienna, Austria

COUNTRY OF AUTHOR: Austria

SOURCE: VACCINE, (8 DEC 2000) Vol. 19, No. 9-10, pp. 1149-1158.

Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE,
KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 0264-410X.

DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 33

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A candidate trivalent **influenza** whole virus vaccine produced in a continuous **mammalian cell** line (Vero), and analogous commercially available egg-derived vaccines, were compared for their ability to induce humoral and cell-mediated immunity in Balb/c mice. Substantial haemagglutination-inhibition titre and high levels of influenza virus-specific IgG were found in all groups of immunized mice, irrespective of the vaccine formulation. The IgG responses were predominantly of IgG1 and IgG2a/2b isotypes. Virus-specific secretory IgA antibodies were detected only in mice immunized intranasally with a live virus, derived either from Vero cells or eggs. T-cell proliferative responses and T-helper 1 type cytokine release was significantly higher in mice immunized with Vero cell-derived influenza vaccine compared to egg-derived vaccine formulations. We have demonstrated that the immunogenicity of the trivalent Vero cell-derived whole influenza virus vaccine was comparable to that of the equivalent egg-derived vaccine, with respect to humoral immune response and was superior with respect to cellular response. (C) 2000 Elsevier Science Ltd. All rights reserved.

L136 ANSWER 29 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:836400 SCISEARCH

THE GENUINE ARTICLE: 369MU

TITLE: Delivering **erythropoietin** through genetically engineered cells

AUTHOR: Bohl D (Reprint); Heard J M

CORPORATE SOURCE: INST PASTEUR, CNRS ERS 572, LAB RETROVIRUS & TRANSFERT GENET, 28 RUE DR ROUX, F-75724 PARIS 15, FRANCE (Reprint)

COUNTRY OF AUTHOR: FRANCE

SOURCE: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (NOV 2000) Vol. 11, No. 11, Supp. [16], pp. S159-S162.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621.
ISSN: 1046-6673.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE; CLIN

LANGUAGE: English

REFERENCE COUNT: 52

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Erythropoietin** (Epo) is a glycoprotein hormone produced by genetic engineering. Many pathologic conditions could benefit from its administration, such as chronic renal failure or hemoglobinopathies. Epo secretion from genetically modified tissues could be proposed to patients only if the protocol is low cost and low risk. For that purpose, retroviral vectors and adeno-associated vectors expressing the Epo cDNA were developed. Gene transfer was performed into skeletal muscles. To avoid polycythemia, a tetracycline-regulated system was used to control the levels of protein secretion in vivo. beta -thalassemias are among diseases that could benefit from an Epo gene transfer. beta -thalassemias are attributable to deficient synthesis of beta -globin and accumulation of unpaired alpha -chains. Stimulation of fetal globin synthesis is one strategy to correct the globin chain imbalance. There is evidence that Epo could play this role. In a mouse model of beta -thalassemia, an adeno-associated vector expressing the Epo cDNA was injected intramuscularly. Epo was secreted continuously during at least 1 yr. Erythropoiesis was improved in those mice by increasing the synthesis of fetal hemoglobin.

L136 ANSWER 30 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:98523 SCISEARCH
THE GENUINE ARTICLE: 159RY
TITLE: Development of optimized vectors for gene therapy
AUTHOR: Nabel G J (Reprint)
CORPORATE SOURCE: UNIV MICHIGAN, DEPT INTERNAL MED & BIOL CHEM, HOWARD
HUGHES MED INST, 1150 W MED CTR DR, 4520 MSRB 1, ANN
ARBOR, MI 48109 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE
UNITED STATES OF AMERICA, (19 JAN 1999) Vol. 96, No. 2,
pp. 324-326.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW,
WASHINGTON, DC 20418.
ISSN: 0027-8424.
DOCUMENT TYPE: Editorial; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23

L136 ANSWER 31 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:251653 SCISEARCH
THE GENUINE ARTICLE: 176UU
TITLE: A novel **mammalian cell** (Vero) derived
influenza virus vaccine: Development, characterization and
industrial scale production
AUTHOR: Kistner O (Reprint); Barrett P N; Mundt W; Reiter M;
SchoberBendixen S; Eder G; Dorner F
CORPORATE SOURCE: BAXTER HYLAND IMMUNO, BIOMED RES CTR, A-2304 ORTH, DENMARK
(Reprint)
COUNTRY OF AUTHOR: DENMARK
SOURCE: WIENER KLINISCHE WOCHENSCHRIFT, (12 MAR 1999) Vol. 111,
No. 5, pp. 207-214.
Publisher: SPRINGER-VERLAG WIEN, SACHSENPLATZ 4-6, PO BOX
89, A-1201 VIENNA, AUSTRIA.
ISSN: 0043-5325.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Influenza** virus for vaccine **production** are
presently produced in embryonated chicken eggs. This conventional standard
methodology is extremely cumbersome; it requires a huge amount of eggs and
an extensive purification to reduce the amount of contaminating egg
proteins and to minimize the risk of allergies against egg albumin. The
shortage of eggs in a pandemic situation, the selection of egg-adapted
variants and the presence of adventitious viruses has emphasized the
necessity for **production** of **Influenza** vaccines on a
well characterized stable cell line. Our established Vero cell technology
has been successfully adapted to large scale **production** of a
variety of **Influenza** virus strains. The **production** in
1200 litre fermenter cultures under serumfree conditions gave antigen
yields comparable to the conventional embryonated egg technology. The
development of a rapid and efficient purification scheme resulted in a
safe high purity vaccine which was at least as immunogenic as conventional
egg-derived vaccines in a mouse model. This vaccine has been shown to be
safe and highly immunogenic in chimpanzees and to be capable of protecting
ferrets against challenge with live virus. Clinical trials have now been
initiated in the UK and Austria.

L136 ANSWER 32 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:660859 SCISEARCH

THE GENUINE ARTICLE: 113NP
TITLE: Control of **erythropoietin** delivery by doxycycline in mice after intramuscular injection of adeno-associated vector
AUTHOR: Bohl D; Salvetti A; Moullier P; Heard J M (Reprint)
CORPORATE SOURCE: INST PASTEUR, LAB RETROVIRUS & TRANSFERT GENET, CNRS, URA 1157, 28 RUE DR ROUX, F-75724 PARIS, FRANCE (Reprint); INST PASTEUR, LAB RETROVIRUS & TRANSFERT GENET, CNRS, URA 1157, F-75724 PARIS, FRANCE; CHU HOTEL DIEU, LAB THERAPIE GEN, NANTES, FRANCE
COUNTRY OF AUTHOR: FRANCE
SOURCE: BLOOD, (1 SEP 1998) Vol. 92, No. 5, pp. 1512-1517. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399. ISSN: 0006-4971.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We reported previously that controlled expression of a foreign gene in response to tetracycline derivative can be accomplished in mice by the autologous transplantation of retrovirus-modified muscle cells. Although regulated systemic delivery of therapeutic proteins from engineered tissues has potential clinical application, the transplantation of muscle cells is not currently feasible in humans. Several studies have shown that a single injection of adenoassociated virus (AAV) vectors into mouse muscle results in long-term expression of reporter genes as well as sustained delivery of proteins into the serum. Because this method is potentially applicable clinically, we constructed an AAV vector in which the expression of the mouse **erythropoietin** (Epo) cDNA is modulated in response to doxycycline. The vector was injected intramuscularly in normal mice. We observed that hematocrit and serum Epo concentrations could be modulated over a 29-week period in response to the presence or absence of doxycycline in the drinking water of these animals. Thus, a regulated gene expression cassette can be incorporated into a single AAV vector, such that intramuscular injection of the vector allows sustained and regulated expression of a desired gene. (C) 1998 by The American Society of Hematology.

L136 ANSWER 33 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:485275 SCISEARCH
THE GENUINE ARTICLE: ZV083
TITLE: Development of a **mammalian cell** (Vero) derived candidate influenza virus vaccine
AUTHOR: Kistner O; Barrett P N (Reprint); Mundt W; Reiter M; Schober-Bendixen S; Doerner F
CORPORATE SOURCE: BAXTER IMMUNO, BIOMED RES CTR, UFERSTR 15, A-2304 ORTH, AUSTRIA (Reprint); BAXTER IMMUNO, BIOMED RES CTR, A-2304 ORTH, AUSTRIA
COUNTRY OF AUTHOR: AUSTRIA
SOURCE: VACCINE, (MAY-JUN 1998) Vol. 16, No. 9-10, pp. 960-968. Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0264-410X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; AGRI
LANGUAGE: English
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Influenza vaccine production** is dependent on the availability of embryonated hen eggs for virus growth. This is an extremely cumbersome system with many disadvantages with respect to

selection of virus variants and presence of adventitious viruses. We have developed an alternative cell culture system which allows rapid production of large volumes of vaccine. The World Health Organisation (WHO) approved Vero cell line was used in serum-free culture to grow a multitude of influenza strains to high titre. This system could be scaled-up to allow vaccine production with a 1200 litre fermenter volume. A purification scheme was developed which resulted in a high purity whole virus vaccine. This was demonstrated to be at least as immunogenic as a conventional egg-derived preparation in a mouse model. (C) 1998 Elsevier Science Ltd. All rights reserved.

L136 ANSWER 34 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:474374 SCISEARCH
THE GENUINE ARTICLE: ZU454
TITLE: Direct sequencing of the HA gene of clinical equine H3N8 influenza virus and comparison with laboratory derived viruses
AUTHOR: Illobi C P; Nicolson C; Taylor J; Mumford J A; Wood J M; Robertson J S (Reprint)
CORPORATE SOURCE: NATL INST BIOL STAND & CONTROLS, DIV VIROL, BLANCHE LANE, POTTERS BAR EN6 3QG, HERTS, ENGLAND (Reprint); NATL INST BIOL STAND & CONTROLS, DIV VIROL, POTTERS BAR EN6 3QG, HERTS, ENGLAND; ANIM HLTH TRUST, CTR PREVENT MED, NEWMARKET, SUFFOLK, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: ARCHIVES OF VIROLOGY, (15 APR 1998) Vol. 143, No. 5, pp. 891-901.
Publisher: SPRINGER-VERLAG WIEN, SACHSENPLATZ 4-6, PO BOX 89, A-1201 VIENNA, AUSTRIA.
ISSN: 0304-8608.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 15

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Equine influenza viruses propagated in the laboratory in alternate hosts such as embryonated hens' eggs or **mammalian cell** culture have been analysed by HA sequencing and antigenically and their sequence compared to the original virus present in clinical material. In contrast to clinically derived human influenza virus which generally grows in MDCK cells without change, the data for equine influenza virus were less clear in that variants of equine virus were derived in both eggs and cells. The study indicated that the current use of eggs for equine **influenza** virus surveillance and vaccine **production** is entirely appropriate, but that care should be exercised when equine **influenza** vaccines are **produced** in eggs or on **mammalian cell** cultures.

L136 ANSWER 35 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:814490 SCISEARCH
THE GENUINE ARTICLE: 129ZL
TITLE: Effects of antipyretics on mortality due to influenza B virus in a mouse model of Reye's syndrome
AUTHOR: Crocker J F S (Reprint); Digout S C; Lee S H; Rozee K R; Renton K; Field C A; Acott P; Murphy M G
CORPORATE SOURCE: DALHOUSIE UNIV, DEPT PEDIAT, 5850 UNIV AVE, HALIFAX, NS B3J 3G9, CANADA (Reprint); DALHOUSIE UNIV, DEPT MICROBIOL & IMMUNOL, HALIFAX, NS, CANADA; DALHOUSIE UNIV, DEPT PHARMACOL, HALIFAX, NS B3H 4H7, CANADA; DALHOUSIE UNIV, DEPT MATH STAT & COMP SCI, HALIFAX, NS, CANADA; DALHOUSIE UNIV, DEPT PHYSIOL & BIOPHYS, HALIFAX, NS, CANADA; IZAAK WALTON KILLAM GRACE HLTH CTR, HALIFAX, NS, CANADA
COUNTRY OF AUTHOR: CANADA

SOURCE: CLINICAL AND INVESTIGATIVE MEDICINE-MEDECINE CLINIQUE ET
EXPERIMENTALE, (AUG-OCT 1998) Vol. 21, No. 4-5, pp.
192-202.
Publisher: CANADIAN MEDICAL ASSOCIATION, 1867 ALTA VISTA
DR, OTTAWA ON K1G 3Y6, CANADA.
ISSN: 0147-958X.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE; CLIN

LANGUAGE: English

REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objectives: To determine the effects of acetylsalicylic acid (ASA) and acetaminophen on mortality due to influenza B infection in neonatal and weanling mice, as well as any synergistic, antagonistic or indifferent effects of the combined antipyretic and virus on mortality in mice pretreated with low doses of an industrial surfactant, Toximul MP8, which has been shown to reproduce many of the features of Reye's syndrome. In vitro studies were done to determine whether ASA or acetaminophen altered the normal, interferon-mediated antiviral responses of **mammalian cells**. The involvement of ASA or other commonly used xenobiotics in the induction of Reye's syndrome following virus illness has not been resolved; to do so, and to elucidate the underlying metabolic mechanism, requires these studies in an animal model.

Design: Prospective animal study.

Animals: Newborn (945) and weanling (840) Swiss white mice, divided into 12 subgroups.

Interventions: Some groups received Toximul MP8 before inoculation with a dose of mouse-adapted human **influenza B** that **produces** 30% mortality (LD30); after infection, each subgroup received either placebo, ASA or acetaminophen. Mortality counts were taken daily. The in vitro effects of the antipyretics on interferon response were determined using standard virology techniques.

Outcome measure: Mortality, analyzed by survival curves (log rank test) or cumulative daily mortality (chi(2) analysis). Plaque-reducing dose (PRD50) was used to determine the outcome of the in vitro analyses.

Results: In neonatal mice, only subgroups given combined treatment with acetaminophen and Toximul MP8 had a statistically significant higher mortality rate than with the mice given influenza B alone. In weanling mice, it appeared that ASA shortened the time until death; however, this difference was not statistically significant. In vitro studies demonstrated that both ASA and acetaminophen decreased the interferon-induced antiviral responses of cultured **mammalian cells**.

Conclusion: Antipyretics have the potential to exacerbate the consequences of a viral infection, although the specific effects are subtle and appear to be age-related.

L136 ANSWER 36 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:912744 SCISEARCH

THE GENUINE ARTICLE: 142AD

TITLE: Analysis of a coded panel of licensed vaccines by
polymerase chain reaction-based reverse transcriptase
assays: A collaborative study

AUTHOR: Maudru T; Peden K W C (Reprint)

CORPORATE SOURCE: US FDA, LAB RETROVIRUS RES, CTR BIOL EVALUAT & RES, BLDG
29A, ROOM 3D08, 29 LINCOLN DR, BETHESDA, MD 20892
(Reprint); US FDA, LAB RETROVIRUS RES, CTR BIOL EVALUAT &
RES, BETHESDA, MD 20892

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF CLINICAL VIROLOGY, (24 JUL 1998) Vol. 11, No.
1, pp. 19-28.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE
AMSTERDAM, NETHERLANDS.

ISSN: 1386-6532.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 21

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: A recent publication reporting the presence of low levels of reverse transcriptase (RT) activity in certain vaccines for human use necessitated that regulatory agencies address the issue of whether this RT activity presented a risk to humans. Detection of low levels of RT activity corresponding to fewer than ten virions became possible with the development of highly-sensitive polymerase chain reaction (PCR)-based RT (PERT) assays. Variations of the PERT assay were developed in three laboratories. These assays were reported as being at least one million-fold more sensitive than conventional RT assays. Objective: To ascertain the sensitivity and reliability of PERT assays in different laboratories and to determine which vaccine samples possessed RT activity. Study design: Coded panels of licensed vaccines together with positive and negative controls was assembled at the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) and distributed to five cooperating laboratories as well as to our laboratory at CBER. Each laboratory carried out their version of the PERT assay and submitted the results to the coordinator at CBER. Results: Results of the PERT analyses carried out in the six laboratories are presented. Five of the six laboratories reported results that were highly consistent. RT activity was detected in live attenuated vaccines that were prepared in chick embryo cells (mumps, measles and yellow fever), but very low or undetectable RT activity was found in vaccines produced in **mammalian cells** (rabies and rubella). **Influenza** vaccines from several **manufacturers** included in the panel displayed the most variability, with different products of this inactivated vaccine having differing amounts of RT activity. Conclusions: Only vaccines produced in chick embryo cells had significant RT activity. Because RT activity was present in the allantoic fluid of uninfected chick embryos and culture medium from chick embryo fibroblasts, the RT activity arises from the cell substrate used for vaccine production. The PERT assays were reliably able to detect the low levels of RT activity in chicken-derived vaccines. (C) 1998 Published by Elsevier Science B.V. All rights reserved.

L136 ANSWER 37 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 96:838959 SCISEARCH
THE GENUINE ARTICLE: VT054
TITLE: AN ESSENTIAL ROLE FOR P300/CBP IN THE CELLULAR-RESPONSE TO HYPOXIA
AUTHOR: ARANY Z; HUANG L E; ECKNER R; BHATTACHARYA S; JIANG C; GOLDBERG M A; BUNN H F; LIVINGSTON D M (Reprint)
CORPORATE SOURCE: DANA FARBER CANC INST, BOSTON, MA, 02115 (Reprint); DANA FARBER CANC INST, BOSTON, MA, 02115; HARVARD UNIV, SCH MED, BOSTON, MA, 02115; BRIGHAM & WOMENS HOSP, DEPT MED, DIV HEMATOL, BOSTON, MA, 02115
COUNTRY OF AUTHOR: USA
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (12 NOV 1996) Vol. 93, No. 23, pp. 12969-12973.
ISSN: 0027-8424.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB p300 and CBP are homologous transcription adapters targeted by the E1A oncoprotein. They participate in numerous biological processes, including

cell cycle arrest, differentiation, and transcription activation. p300 and/or CBP (p300/CBP) also coactivate CREB. How they participate in these processes is not yet known. In a search for specific p300 binding proteins, we have cloned the intact cDNA for HIF-1 alpha. This transcription factor mediates hypoxic induction of genes encoding certain glycolytic enzymes, **erythropoietin** (Epo), and vascular endothelial growth factor. Hypoxic conditions lead to the formation of a DNA binding complex containing both HIF-1 alpha and p300/CBP. Hypoxia-induced transcription from the Epo promoter was specifically enhanced by ectopic p300 and inhibited by **E1A** binding to p300/CBP. Hypoxia-induced VEGF and Epo mRNA synthesis were similarly inhibited by **E1A**. Hence, p300/CBP-HIF complexes participate in the induction of hypoxia-responsive genes, including one (vascular endothelial growth factor) that plays a major role in tumor angiogenesis. Paradoxically, these data, to our knowledge for the first time, suggest that p300/CBP are active in both transformation suppression and tumor development.

L136 ANSWER 38 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 94:701915 SCISEARCH
THE GENUINE ARTICLE: PP274
TITLE: EFFICIENT PRODUCTION OF BIOLOGICALLY-ACTIVE HUMAN
RECOMBINANT PROTEINS IN HUMAN LYMPHOBLASTOID-CELLS FROM
INTEGRATIVE AND EPISOMAL EXPRESSION VECTORS
AUTHOR: LOPEZ C (Reprint); DECHESNAY A; TOURNAMILLE C; BENGHANEM
A; PRIGENT S; DROUET X; LAMBIN P; CARTRON J P
CORPORATE SOURCE: INST NATL TRANSFUS SANGUINE, 6 RUE ALEXANDRE CABANEL,
F-75015 PARIS, FRANCE (Reprint)
COUNTRY OF AUTHOR: FRANCE
SOURCE: GENE, (21 OCT 1994) Vol. 148, No. 2, pp. 285-291.
ISSN: 0378-1119.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The ability of human lymphoblastoid cells to secrete large amounts of biologically active human hematopoietic growth factors from **adenovirus**-based expression vectors was investigated. The gene for human **erythropoietin** (EPO) was inserted into integrative (pTS39) and episomal (pTS53) vectors. Cell clones, originating from pTS39 or pTS53-transfected and stably selected cells, secreted recombinant human EPO (re-hEPO) at similar levels. The highest production, 60 u/10(6) cells per 24 h, was obtained from a subclone of pTS39-transfected cells: grown in nonselective medium. The re-hEPO was shown to be biologically active in vivo by incorporation of Fe-59 into red blood cells of polycythemic mice and in vitro by the proliferative response of the EPO-dependent cell line UT7. The purified protein of 36 kDa in SDS-PAGE slightly differed from re-hEPO from CHO cells. pTS39 vector was integrated at 15-30 copies per genome, whereas the pTS53 vector replicated at 10 copies per cell. Genes encoding human interleukin-3 (IL-3) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were also expressed in the integrative system as biologically active growth factors, demonstrating that our host-vector system allows the expression of any little gene or cDNA and efficient secretion of the re-protein produced.

L136 ANSWER 39 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 93:696712 SCISEARCH
THE GENUINE ARTICLE: MG307
TITLE: RESCUE OF AN INFLUENZA-A VIRUS WILD-TYPE PB2 GENE AND A
MUTANT DERIVATIVE BEARING A SITE-SPECIFIC
TEMPERATURE-SENSITIVE AND ATTENUATING MUTATION
AUTHOR: SUBBARAO E K (Reprint); KAWAOKA Y; MURPHY B R

CORPORATE SOURCE: NIAID, INFECT DIS LAB, RESP VIRUSES SECT, BETHESDA, MD, 20892 (Reprint); ST JUDE CHILDRENS HOSP, DEPT VIROL & MOLEC BIOL, MEMPHIS, TN, 38101

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF VIROLOGY, (DEC 1993) Vol. 67, No. 12, pp. 7223-7228.
ISSN: 0022-538X.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: ENGLISH

REFERENCE COUNT: 19

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Live attenuated **influenza** A virus vaccines are currently **produced** by the transfer of attenuating genes from a donor virus to new epidemic variants of influenza A virus, with the selection of reassortant viruses that possess the protective antigens (i.e., the two surface glycoproteins) of the epidemic virus and the attenuating genes from the donor virus. The previously studied attenuated donor viruses were produced by conventional methods such as passage of virus at low temperature or chemical mutagenesis. The present paper describes a new strategy for the generation of a donor virus bearing an attenuating, non-surface-glycoprotein gene. This strategy involves the introduction of attenuating mutations into the cDNA copy of the PB2 polymerase gene by site-directed mutagenesis, transfection of in vitro RNA transcripts of PB2 cDNA, and recovery of the transfected PB2 gene into an infectious virus. An avian-human influenza A virus PB2 single-gene reassortant virus (with an avian influenza A virus PB2 gene) that replicates efficiently in avian tissue but poorly in **mammalian cells** was used as a helper virus to rescue a transfected synthetic RNA derived from a human influenza A virus PB2 gene. The desired human influenza A virus mutant PB2 transfectant was favored in this situation because the avian influenza A virus PB2 gene restricts viral replication in **mammalian cells** in culture, the system used for rescue, thereby providing strong selection for the virus bearing the human influenza A virus PB2 gene. We validated the feasibility of this approach by rescuing the PB2 gene of the wild-type influenza A/Ann Arbor/6/60 virus and a mutant derivative that had a single amino acid substitution introduced at position 265 by site-directed mutagenesis. Previously, this amino acid substitution had been shown to specify both a temperature-sensitive (ts) and an attenuation (att) phenotype. The rescued mutant 265 PB2 transfectant virus exhibited the ts and att phenotypes, which confirms that these phenotypes were specified by this single amino acid substitution. The transfectant virus was immunogenic and protected hamsters from subsequent challenge with wild-type virus. The cDNA copy of this influenza A/Ann Arbor/6/60 virus mutant 265 PB2 gene will be used as a substrate for the introduction of additional attenuating mutations by site-directed mutagenesis.

L136 ANSWER 40 OF 43 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 91:546176 SCISEARCH

THE GENUINE ARTICLE: GH256

TITLE: A NOVEL METHOD FOR INCREASED YIELD OF IMMUNOCOMPETENT VIRUS FOR VACCINE PRODUCTION

AUTHOR: QURESHI A A (Reprint)

CORPORATE SOURCE: UNIV BAHRAIN, DEPT BIOL, POB 32038, ISA TOWN, BAHRAIN (Reprint)

COUNTRY OF AUTHOR: BAHRAIN

SOURCE: WORLD JOURNAL OF MICROBIOLOGY & BIOTECHNOLOGY, (1991) Vol. 7, No. 5, pp. 567-570.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: AGRI

LANGUAGE: ENGLISH

REFERENCE COUNT: No References Keyed

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cultured **human cells** exposed to the pesticide emulsifier Atlox, 6 to 8 h prior to infection with **influenza A virus**, increased virus **production** approximately 10-fold. Antibodies against the 'enhanced virus' neutralized plaque formation and reacted equally well with non-enhanced virus in serological tests (haemagglutination-inhibition and radioimmunoassays). The procedure has great potential in cutting costs of production for some virus vaccines.

L136 ANSWER 41 OF 43 WPIDS (C) 2002 THOMSON DERWENT
 ACCESSION NUMBER: 2002-147620 [19] WPIDS
 DOC. NO. CPI: C2002-045762
 TITLE: **Adenoviral** coat protein which permits production of **adenoviral** vectors that bind and infect host cells not naturally infected by **adenovirus**, comprises various non-native ligands.
 DERWENT CLASS: A96 B04 D16
 INVENTOR(S): BROUGH, D E; EINFELD, D; KOVESDI, I; LIZONOVA, A; ROELVINK, P W; WICKHAM, T J
 PATENT ASSIGNEE(S): (GENV-N) GENVEC INC
 COUNTRY COUNT: 96
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001092549	A2	20011206	(200219)*	EN	45
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001065154	A	20011211	(200225)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001092549	A2	WO 2001-US17391	20010530
AU 2001065154	A	AU 2001-65154	20010530

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001065154	A Based on	WO 200192549

PRIORITY APPLN. INFO: US 2000-631191 20000802; US 2000-208451P
 20000531

AB WO 200192549 A UPAB: 20020321
 NOVELTY - A recombinant **adenoviral** (AV) coat protein (I) comprising a non-native ligand (NNL) which binds to a substrate, where an AV vector having the recombinant AV coat protein lacks native binding to coxsackievirus and **adenovirus** receptor (CAR), or a recombinant coat protein (II) comprising a NNL which binds to a matrix metalloproteinase (MMP), and a non-native amino acid sequence, is new.
 DETAILED DESCRIPTION - A recombinant **adenoviral** (AV) coat protein (I) comprising a non-native ligand (NNL) which binds to a substrate, where an AV vector having the recombinant AV coat protein lacks native binding to coxsackievirus and **adenovirus** receptor (CAR), or a recombinant coat protein (II) comprising a NNL which binds to a matrix metalloproteinase (MMP), and a non-native amino acid sequence, is new. (I) comprises a NNL which binds to a substrate chosen from

melanocortin receptor (MCR), alpha v, alpha v beta 3, alpha v beta 6, alpha 4, alpha 5, alpha 9 integrins, CD13, melanoma proteoglycan, membrane dipeptidase (MDP), TAG2 antigen, an antigen binding site of a surface immunoglobulin receptor of B-cell lymphomas, type I interleukin 1 (IL-1) receptor, human immunodeficiency virus type 1 (HIV-1), envelope glycoprotein (gp120), atrial natriuretic peptide (ANP) receptor, **erythropoietin** (EPO) receptor, thrombopoietin (TPO) receptor, carcino-embryonic antigen (CEA) receptor, EpCAM, CD40, prostate-specific membrane antigen (PSMA), endoglin, epidermal growth factor receptor (EGFR), HER2 and an extracellular matrix component.

INDEPENDENT CLAIMS are also included for the following:

- (1) a nucleic acid (NA) encoding (I) or (II);
- (2) an AV vector (III) comprising (I) or (II);
- (3) an AV vector (IV) comprising a modification, where the modified AV vector elicits less reticulo-endothelial system (RES) clearance in a host animal than a corresponding wild-type **adenovirus**;
- (4) a system (V) comprising a cell having a non-native cell-surface receptor (CSR), and a virus having a NNL which binds the non-native CSR of the cell;
- (5) a CSR (VI) comprising a first and second domain, where the first domain (D1) binds an AV vector having one or more chimeric AV coat proteins, and the second domain (D2) facilitates internalization of the AV vector into a cell;
- (6) a non-native, non-**adenovirus** CSR (VII) comprising D1 and a second domain which is a glycerol-phosphate-inositol linkage;
- (7) a cell comprising (VI) or (VII); and
- (8) controlling (VIII) gene expression, by administering to an animal a selectively replication competent AV vector having a first non-native NA, operably linked to a promoter, and a targeting agent.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Gene therapy.

AV vectors comprising the hemagglutinin (HA) tag incorporated into the AV coat protein were generated. One clone was generated such that binding to coxsackievirus and **adenovirus** receptor (CAR) was ablated (AdL asterisk). A clone also was generated such that binding to alpha v integrin by the penton based was ablated (AdL.PB asterisk). An additional clone was generated such that native binding to CAR and alpha v integrin was ablated (AdL.PB asterisk F asterisk). Each vector clone contained the luciferase reporter gene driven by the cytomegalovirus (CMV) promoter. Two types of melanoma tumors, B16F0 tumors expressing (B16F0-HA) and not expressing (B16F0) the single-chain antibody directed to HA, a non-native cell-surface receptor, were grown in nude mice. Approximately 1010 particles of AdL asterisk , AdL.PB asterisk F asterisk , and AV vector containing the luciferase gene but not HA tag (ADL) were administered to each tumor by intratumoral injection. Transduction was quantified by luciferase assay. Transduction of tumors bearing the non-native receptor with AdL and AdL asterisk was slightly greater than tumors not comprising the non-native receptor. However, the transduction of B16F0-HA tumors expressing the non-native receptor with AdL.PB asterisk F asterisk was 40-fold greater than transduction of B16F0 tumors not expressing the non-native receptor. The results demonstrated the ability of the gene transfer vector to transduce cells of the system more efficiently than the cells not comprising the non-native receptor.

USE - (V) is useful for propagating a virus and also for assaying gene function. The cell of the system is infected with gene transfer vector, preferably an **adenovirus** encoding one or more gene products and comprising a ligand that binds the non-native CSR of the cell and assayed for an activity of the gene products. The system is also useful for isolating a NA encoding a product comprising a desired property, by infecting the cells of the system with a library of AV vectors, where each member of the library comprises a ligand that binds the non-native CSR of the cell and a NA encoding a product comprising a potentially desired property. Cells comprising the library are assayed for

desired property and the AV vector comprising the NA encoding the product comprising the desired property is isolated. Further the system is useful for identifying functionally related coding sequences. Cells are infected with library of AV vectors, each comprising a ligand that binds the non-native cell-surface of the cell, a first heterologous DNA encoding a first gene product, which is common to each vector, and a second heterologous DNA encoding a second gene product, which varies between the vectors, and the activity of the gene products encoded by the vectors is compared with the activity of the first gene product encoded by vector comprising the first heterologous DNA but not comprising the second heterologous DNA. The vector does not bind to the cell not having the non-native CSR. Cell comprising (VI) is useful for assaying for gene function and isolating a NA encoding a product comprising a desired property. (III) or (IV) comprising a non-native NA encoding a therapeutic agent such as anti-tumor agent, preferably tumor necrosis factor and a second non-native NA encoding an agent that facilitates imaging and a targeting agent is useful for treating an animal. (All claimed). The therapeutic agent can be used to treat cancer of the brain, lung, ovary, breast and prostate.

ADVANTAGE - The AV vector displaying the ligand for alpha v beta 3 integrin and lacking native binding have a longer half-life in serum compared to vectors where native binding was ablated and demonstrate decreased tropism to non-cancerous tissue, such as kidney and lung. The non-native amino acid sequence increases efficiency by decreasing non-target cell transduction by the AV vector and by decreasing recognition of the AV vector by the immune system.
Dwg.0/0

L136 ANSWER 42 OF 43 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-410916 [44] WPIDS
CROSS REFERENCE: 2001-357956 [38]
DOC. NO. CPI: C2001-124565
TITLE: Producing a virus or viral protein useful as a vaccine against viral pathogens, comprises introducing a sequence encoding an E1 gene product to PER.C6 cells (ECACC 96022940).
DERWENT CLASS: B04 D16
INVENTOR(S): PAU, M G; SCHOUTEN, G J; UYTDEHAAG, A G C M
PATENT ASSIGNEE(S): (CRUC-N) CRUCCELL HOLLAND BV
COUNTRY COUNT: 26
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1108787	A2	20010620	(200144)*	EN	48
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1108787	A2	EP 2000-204190	20001124

PRIORITY APPLN. INFO: EP 1999-203983 19991126
AB EP 1108787 A UPAB: 20010809

NOVELTY - Producing a virus and/or viral proteins other than adenovirus or adenoviral proteins for use as a vaccine, comprises providing a cell with at least a sequence encoding a gene product of the E1 gene or a derivative of an adenovirus, or with a nucleic acid encoding the virus and/or viral proteins, and culturing the cell for the expression of the virus or viral proteins.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a virus or a viral protein for use in a vaccine obtained by the method that is free of any non-human mammalian proteinaceous material;
- (2) a **human cell** having a sequence encoding at least E1 protein of an adenovirus or its functional derivative, homologue or fragment of its genome, which cell does not produce structural adenoviral proteins and having a nucleic acid encoding a virus or at least one non-adenoviral protein;
- (3) a kit for determining activity of a protease in a sample comprising at least one viral protein or virus obtained by the method;
- (4) concentrating (M1) **influenza** virus under conditions capable of at least in part preserving virus infectivity, comprising obtaining a cell-cleared supernatant containing the virus from a culture of cells, and ultrafiltrating the supernatant under low shear conditions; and
- (5) concentrated infectious **influenza** virus or its derivatives obtained by the method of M1.

ACTIVITY - Virucide.

MECHANISM OF ACTION - Vaccine.

Eighteen adult female ferrets were divided in 3 groups of 6 as follows: Group 1 received the egg-derived test vaccine intramuscularly (i.m.); Group 2 received the PER.C6 derived test vaccine i.m.; and Group 3 received the test vaccine diluent only. The 3 groups were challenged with A/Sydney/5/97, and on day 0 and 28, test vaccines were administered. On day 56, all ferrets were infected intranasally with 0.5 ml of the A/Sydney/5/97 challenge virus at TCID50 103. Nasal washes were performed and inflammatory cell counts, temperature and weights of the ferrets were monitored once daily from day 57-63. Animals were sacrificed on day 63, and nasal wash recovery cell count was performed using Trypan blue exclusion assay. Virus titer obtained from the nasal wash samples was determined by measuring viral recovery on Madin-Darby canine kidney cells. Hemagglutination inhibition analysis on serum samples on day 0, 28, 56 and 63 showed that PER.C6 derived test vaccine was effective.

USE - The method and the cell are useful for producing a vaccine against viral pathogens of vertebrates, especially humans. The **human cell** having a sequence encoding at least one E1 protein of an adenovirus or its functional derivative, homologue or fragment in its genome and which does not produce structural adenoviral proteins for the production of a virus or at least one viral protein for use in a vaccine. The cell is also useful in generating an **influenza** virus strain that does not grow very efficiently on embryonal eggs. The virus or the viral protein can be used for determining protease activity in a sample.

ADVANTAGE - The new method overcomes problems associated with previous methods of vaccine production, such as difficulty in purification and extensive safety measures against contamination. The new method of vaccine production in mammalian cells allows large-scale continuous production of viruses to a high titer, where the cells can be cultured under defined serum free conditions and show improved capability for propagating virus.

Dwg.0/33

L136 ANSWER 43 OF 43 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-204005 [17] WPIDS
DOC. NO. CFI: C1999-059340
TITLE: New replication deficient **adenovirus** bearing deletions of the **E1a** and **E3** regions - containing a single packaging signal sequence and **E1a** enhancer sequence, the **E1a** deletion has unique cleavage sites and is useful as a gene therapy vector.
DERWENT CLASS: B04 D16

INVENTOR(S): BLAZING, M A; GEORGE, S E
PATENT ASSIGNEE(S): (UYDU-N) UNIV DUKE
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5880102	A	19990309	(199917)*		148

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5880102	A	US 1995-374483	19950117

PRIORITY APPLN. INFO: US 1995-374483 19950117

AB US 5880102 A UPAB: 19990503

NOVELTY - A replication deficient **adenovirus** bearing deletions of the **E1a** and E3 regions and comprising a single packaging signal sequence and **E1a** enhancer sequence, where the sequences are at the 3' end of the **adenovirus** and the **E1a** deletion contains at least one **PacI**, **Clal**, **XbaI** or **BstBI** cleavage site, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) an **adenovirus** bearing deletions of the **E1a** and E3 regions and comprising an **E1a** enhancer sequence and packaging signal sequence at the 3' end, where the **adenovirus** is Ad:Pac-beta Gal, Ad:Pac-beta Gal/gfp or In340 E3D; (2) a replication deficient **adenovirus** comprising a recombination product of In340 E3D, Ad:Pac-beta Gal or Ad:Pac-beta Gal/gfp and plasmid pGEM Age I CMV new or pGEM Cla CMV(+) Pac comprising in operable linkage, a sequence encoding a selectable marker or other desired protein; (3) a cell containing any of the new **adenoviruses**; (4) a plasmid replicable and selectable in bacteria, devoid of **adenoviral E1a** enhancer and packaging signals, comprising an **adenoviral** terminal repeat, a promoter/multiple cloning site (MCS)/poly A unit (I) and an **adenoviral** recombination sequence, the terminal repeat is 5' to (I), the plasmid also comprises a unique restriction site permitting direct ligation with an **adenovirus** that is present 3' to (I) and the recombination sequence; and (5) a plasmid as in (4) excluding the **adenoviral** recombination sequence.

USE - The replication deficient viral vectors can be used in gene therapy regimens to effect the transfer of genes encoding molecules of therapeutic importance, including isoforms of the nitric oxide synthetase (NOS) gene (brain, endothelial and microphage NOS), the cystic fibrosis chloride channel (CFTR) gene, the dystrophin gene, the LDL receptor gene and the **erythropoietin** gene. The NOS isoforms can be used in vascular applications or in cancer therapy (microphage NOS). The NOS gene can be introduced into vein grafts prior to their use as coronary artery bypass grafts. A NOS containing **adenovirus** can also be used following coronary angioplasty to prevent retinosis and to treat atherosclerotic arteries.

ADVANTAGE - The system has a screening capacity built into it for determining the success of a particular recombination or ligation event. The system eliminates the use of a wild type virus to form the vector backbone (prior art), which is hazardous to use as it is replication efficient, giving it a growth advantage over recombinant virions. The system also simplifies the cloning of genes into plasmid vectors, it makes the use of either ligation or overlap recombination in the generation of a recombinant virus possible and eliminates the use of cell replication efficient viral forms. The levels of gene expression are superior to those of existing vectors and can be used at titers significantly lower than

those required for existing systems, therefore reducing/eliminating the potential for adverse (cytotoxic or inflammatory) effects. The system allows the introduction of two coding sequences (e.g. cDNAs) into the same **adenovirus**.
Dwg. 3 107

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